In addition, Applicant acknowledges that claims 66-68 are free from the art. Claims 66-68 are only rejected under 35 U.S.C. § 112, first and second paragraphs. Applicant addresses these rejections herein.

Claims 66-80 are pending.

Claim 66 has been amended to make clear to what each component of the agents of this claim is attached.

Allowed claims 79 and 80 have been amended to make clear that the H_c domain of a botulinum toxin may be either removed or modified when attached to substance P. The amended claims are fully supported by the specification. For example, the last paragraph on page 15 states: "The clostridial neurotoxin component may comprise only fragments of the entire neurotoxin. For example, in one embodiment, the H_c of the neurotoxin is removed or modified." In addition, the second full paragraph on page 17 states: "In an additional preferred embodiment of the present invention, the agent comprises botulinum toxin neurotoxin type A, wherein the H_c of the botulinum neurotoxin type A is modified, more preferably removed or deleted, and the remaining toxin (i.e. with the H_c removed) is then covalently coupled to substance P."

The amendments to claim 66 and to allowed claims 79 and 80 have not been presented for any reason related to statutory requirements for patentability and/or the claims as a whole have not been narrowed. Hence, the presently pending claims are not subject to the rule set forth in Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki, Co., 56 USPQ 2d 1865 (Fed. Cir. 2000).

Rejection Under 35 U.S.C. 112, First Paragraph

Claims 67 and 68 have been rejected under 35 U.S.C 112, first paragraph.

The Examiner acknowledges that the specification enables an agent comprising a clostridial neurotoxin component covalently attached to substance P (Office Action, page 3), but apparently believes that the specification does not provide enablement for an agent comprising a clostridial neurotoxin component covalently attached to a "precursor" of substance P or an "analogue" of substance P. The Examiner alleges that it is not known or expected that precursors and analogs of substance P will function in the same manner as substance P (Office Action, page 3).

Applicant respectfully disagrees and traverses the rejection. Applicant respectfully submits that the claims are properly enabled by the specification.

Although the Examiner believes that one skilled in the art would require additional guidance in order to make and use the invention as claimed, Applicant respectfully disagrees.

THE LEGAL STANDARD FOR ENABLEMENT

Under 35 U.S.C. § 112, first paragraph, Applicants need only provide enough information to one of ordinary skill in the art to practice the invention as claimed. In re Eynde, 480 F.2d 1364, 178 U.S.P.Q. 470 (C.C.P.A. 1973) ("That statutory requirement is fulfilled where one possessed of the knowledge had by one skilled in the art could use the invention given the specification disclosure without undue experimentation."). Furthermore, while "the scope of enablement varies inversely with the degree of unpredictability involved," Applicant does not have to disclose an example of every species covered by a claim. In re Angstadt, 537 F.2d 498, 502-503, 190 U.S.P.Q. 214 (C.C.P.A. 1976). "It is not necessary that patent applicant test all embodiments of his invention; what is necessary is that he provide disclosure sufficient to enable one skilled in the art to carry out the

invention commensurate with the scope of his claims." Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd. 927 F.2d 1200 (1991).

The requirements of 35 U.S.C. § 112, first paragraph are fulfilled where one skilled in the art could make and use the invention given the specification disclosure without undue experimentation.

The determination of what constitutes undue experimentation in a given case requires "the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art" Ansul Co. v. Uniroyal, Inc., 448 F.2d 872, 169 USPQ 759 (2d. Cir. 1961), cert. denied, 404 U.S. 1018, 172 USPQ 257 (1972)).

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention (Ex parte Forman, et al. 230 USPQ 546, 547 (BPAI 1986)). "The enablement requirement is met if the description enables any mode of making and using the claimed invention." Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533 (Fed.Cir.1991).

In the instant application, Applicant describes agents for treating pain. One example is an agent that comprises botulinum toxin covalently attached to substance P. Applicant discloses that precursors and analogues of substance P can similarly be attached to a Clostridial neurotoxin to reduce pain. Despite the description in the specification, the Examiner is unnecessarily and unfairly constraining Applicant to claim a specific species of an agent (e.g., Clostridial neurotoxin covalently coupled to substance P). According to In re Angstadt, Applicant does not

need to disclose every species of agent that is covered by the claims merely because the field is "unpredictable".

Read in the context of the specification, one of ordinary skill in the art would readily understand the meaning of "substance P precursors" or "substance P analogues" as claimed. Applicant has provided enabling examples of such precursors and analogs (e.g., page 26-27; Table I).

Applicant has discovered that an agent that comprises a Clostridial neurotoxin coupled to substance P is effective in treating pain. As discussed above, based on Applicant's disclosure, knowing that such an agent is effective, those of ordinary skill in the art would readily be able to make and use substance P precursors and analogues using routine experimentation. Again, no undue experimentation is required nor is "ingenuity beyond that to be expected of one of the ordinary skill in the art." In re Angstadt, 537 F.2d 498, 190 U.S.P.Q. 214 (C.C.P.A. 1976), citing Fields v. Conover, 443 F.2d 1386, 1390-91, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971).

Given that Applicant discloses how to make the agents of the invention (e.g., Example 1, page 37), how to administer the agents of the invention to treat pain (e.g., page 32, line 18 to page 34, line 21), and several specific examples of substance P precursors and analogues (e.g., pages 26-27, Table I), Applicant respectfully submits that any experimentation necessary to practice the claimed invention would be routine and not undue.

The level of skill in the art is high. Typically, persons skilled in the art who are manufacturing the agents of the invention are well-versed in protein chemistry and/or recombinant DNA technology. As disclosed in Example 1, the synthesis of the agents of the invention is performed using methods that are well known in the art. In addition, persons skilled in the art who administer the agents of the invention are typically physicians

with several years of medical experience. Given Applicant's disclosure of how and where to administer the agents of the invention, one of skill in the art would not have to unduly experiment to administer agents of the invention that comprise precursors or analogues of substance P.

The Examiner believes that allegedly it is not expected to be known whether the agent containing substance P analogues or precursors work in the same manner as the agent containing substance P. In that regard, the Examiner bases his opinion on the indication that allegedly there is no data indicating an agent comprising a Clostridial neurotoxin component covalently attached to the precursor or analogue of substance P actually being made and used for treating pain. Applicant reminds the Examiner that illustrative examples are not required as long as objective enablement is satisfied. In re Wright, 999 F.2d 1557, 1561 (Fed.Cir.1993).

Instead of assuming that the claimed invention is not enabled based on an alleged lack of experimental data, which is not required to enable the invention, the Examiner should identify some specific proof that the use of the agents of the invention is more unpredictable or more unreliable with respect to precursors or analogues of substance P than it is with substance P.

In addition, Applicant notes that the targeting moieties, such as substance P, or analogues or precursors thereof, facilitate the specificity of the cell types to which the agents of the invention bind (e.g., the targeting moiety targets specific receptors expressed by the cells of interest). Once the agents of the invention bind to the cell, the neurotoxin component translocates into the cell where it inhibits secretion from the cell. Accordingly, without substantive proof or evidence to the contrary, there is no reason to expect that the agents that comprise analogues or precursors of substance P would

be less effective in treating pain than agents that comprise substance P since the treatment of pain results from the effects of the neurotoxin.

However, in further support of Applicant's position, Applicant notes that U.S. Patent No. 5,891,842, (the '842 patent), which is incorporated into the specification of the patent application by reference, discloses data showing that precursors of substance P (e.g., substance P-G) are fully active (e.g. column 22, lines 24-29). Indeed, it is stated that "the dodecapeptide SP-Glycine (SP-G) yielded an intensity and duration of [analgesic] effect which were indistinguishable from that produced by the combination of MS and SP ..." (column 19, lines 57-60). Accordingly, the '842 patent provides data that demonstrates similar activities between substance P and precursors thereof.

In view of the foregoing, Applicant respectfully submits that claims 67 and 68 are enabled, and respectfully requests the Examiner to withdraw the rejection.

Rejection Under 35 U.S.C. 112, Second Paragraph

The Examiner has rejected claims 66-68 under 35 U.S.C 112, second paragraph. The Examiner has rejected claim 66 because of his belief that it is unclear to what the proteolytic domain is covalently attached (Office Action, page 5).

Applicant has amended claim 66 as set forth above. Applicant respectfully submits that claim 66 is definite. In that regard, claim 66 now indicates that the proteolytic domain is attached to a translocation domain that is attached to substance P.

The Examiner has rejected claims 67 and 68 because allegedly the terms "analogs" and "precursors" of substance P are

indefinite. In particular, the Examiner states that it is unclear what kind of peptides are intended for the precursors or analogues of substance P.

Applicant respectfully disagrees and respectfully traverses the rejection.

As set forth in the MPEP § 2173.02, definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The claims must be read in light of the specification. "[I]f the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more," Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed.Cir.1985)). Breadth of a claim is not to be equated with indefiniteness. (In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971), cited in MPEP 2173.04).

Applicant respectfully submits that the Examiner has improperly interpreted the breadth of claims 67 and 68 as an indefiniteness issue. Applicant has disclosed several substance P precursors and analogues (e.g., pages 26-27, Table I). Applicant respectfully submits that one skilled in the art readily understand the meaning of "precursor" and "analogue" of substance P. In that regard, a "precursor" of substance P is a peptide that may be modified, naturally or synthetically, to

become substance P. An "analogue" of substance P is a compound that possesses enough physical similarity that it retains at least one biological activity of substance P (e.g., the ability to bind to a substance P receptor).

Applicant also respectfully submits that the '842 patent indicates the meaning of these terms as understood by persons skilled in the art. For example, column 12, line 66 of the `842 patent states: "The history, isolation, identification, and synthesis of substance P and its representative family members including precursors, fragments, analogs and/or derivatives have been described in detail previously herein and are conventionally known in the art through numerous scientific publications over many years." Further, table 4 in the '842 patent discloses a number of representative substance P precursors and analogs.

Thus, in view of the foregoing, Applicant respectfully submits that claims 66-68 are definite, and respectfully requests the Examiner to withdraw the rejection.

In view of the above, Applicant submits that the presently pending claims, 66 to 68 and previously allowed claims 69 and 80 are in condition for allowance.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned representative invites the Examiner to telephone Greg S. Hollrigel, Ph.D., at the number provided below.

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Reg. No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

Attachment: Version with Markings to Show Changes Made

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the following pending claim as indicated:

66. (Amended) An agent for treating pain, the agent comprising[:]

[(a)] a botulinum toxin type A proteolytic domain covalently attached to[;]

[(b)] a botulinum toxin type A translocational domain[, and

(c) substance P covalently attached to the translocational domain] that is covalently attached to substance P.

Please amend the following allowed claims as indicated:

79. (Amended) An agent for treating pain comprising a botulinum toxin covalently coupled to substance P, wherein an H_c of the botulinum toxin has been removed or modified.

80. (Amended) An agent for treating pain comprising a botulinum toxin serotype A covalently coupled to substance P, wherein an H_c of the toxin has been removed or modified, the agent treats pain by acting on [the] a projection neuron.